Davies, David R. 1999 A

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David R. Davies, Ph.D.

This is the first interview with Dr. David R. Davies, 22 November 1999, in his office on the third floor of Building 5, National Institutes of Health, Bethesda, Maryland. The interviewer is Dr. Buhm Soon Park.

Please note: Some names unable to verify

Park: What brought you to NIH and what was your first impression?

Davies: Well, when I left Cal Tech to go back to England in 1954, I visited my very good friend who had worked with me at Cal Tech. His name was Joe Blum. He's retired now. He's a professor of physiology down at Duke. And he lived here with his wife and young child, and they lived just off East-West Highway. And we went to visit them, and he worked at the Navy. While I was there, I came into NIH, which they had just finished the Clinical Center, and Jack Dunitz, who was a very well-known crystallographer, had agreed to join Alex Rich's group. Alex wasn't here yet. And so there was this brand-new building. You know, it looks pretty shoddy now, but at that time it was a most impressive building. And Jack was there, and the equipment was beginning to arrive.

Park: X-ray equipment.

Davies: Well, it was electrophoresis, I think, that had come first, one of these big liquid electrophoresis machines, and he was--I think he was using that as a tabletop or something at the time because he was really a crystallographer. He was interested in small molecules, and I don't think he ever got involved or shared Alex's interest in larger or macromolecules of biological interest.

So, that was in 1954, and then I went back to England for a year. Then I came back here in 1955, and it was December 1955. And Gary Felsenfeld had just arrived, and at the time that I came here; I remember we stayed for several weeks till we found an apartment in Alex Rich's house, which was down on MacArthur Boulevard. And Alex was in Cambridge. He had persuaded the NIH to let him go and visit Francis Crick in Cambridge. And he was staying in Francis Crick's house in Cambridge.

Well, I've got to go back a little step. This was in 1955, and 1955 was a banner year for collagen, a banner year for collagen. And, you know, collagen is probably the most abundant protein, and there had been several structures of collagen, related to collagen. One was the structure of polyproline, which came from a group headed by Sir John Randall, who was probably Professor Randall at that time, and with Pauline Harrison, who eventually became a very well-known crystallographer. And they determined from fiber diffraction the structure of polyproline, which was just a single-stranded molecule. But because the proline restricts the number of possibilities, I mean, it was a fairly rigid structure. And then, shortly afterwards, I think it was Rich and Crick, or Crick and Rich, looked at the structure of polyglycine, and polyglycine had strands of glycine for polyglycines, and they made hydrogen bonds to their neighbors, and they were arranged in groups of three. One was called--one group was different from the other group, depending on which ones you took. And it turned out that these polyglycines had the same helical--I mean, if you took a single strand, they had the same helical parameters as polyproline. Now, collagen has the sequence *gly pro hi pro*, where the *gli* is absolutely fixed every first position and then you can have proline or hydroxyproline at either of the next two positions, or you can have other amino acids. And so, of course, they realized this, Crick and Rich, and they constructed a model for this in which they took three strands, each with a sequence that could be *gly pro hi pro*, so if it was the same twist as polyproline, then it could, it was constrained. They used a polyproline sequence structure and they had every third residue of glycine, and the glycine made a contact with the main chain of another, with another main chain, and that's what held the whole thing together. So it was three strands. The polyproline structure had a threefold repeat, so you went from three residues and then you were above the first---one, two, three, and you were above the first one, and we kept on doing that. And the collagen structure initially had something like that, and I think that was basically the original structure that, although I've got to be careful what I say here because I don't remember all the history now, was the structure Ramachandran had proposed, G.N. Ramachandran working in Madras, for collagen. But since there were well-defined diffraction patterns for collagen, Rich and Crick realized that you would have to twist the collagen a little bit, and it was that twist that made their structure different. They only had one hydrogen bond per glycine, whereas the, I think the Ramachandran structure had one extra hydrogen bond, but it didn't really fit with the diffraction data as well. And I think that Rich and Crick's structure has stood the test of time. Well, all this was happening. This is tremendously exciting stuff, you know, and the alpha helix had been worked out, the beta sheet had been determined by Pauling, and the DNA structure had been worked out by Watson and Crick. So there they were in Cambridge, Rich and Crick, and they worked out the structure of collagen, made a very, in my opinion, a very important step forward, although collagen is sort of inert, and so there's been less interest in collagen, perhaps, than in, naturally, than in DNA or in the alpha helix structure. And Alex Rich refused to come back. He was scientifically on a high here, and he was doing so well in his collaboration with Crick that I think his passport even expired.

Park: Did he want to stay in Cambridge?

Davies: The story I heard was that he... Well, no, no. He just wanted to stay there until, I mean, this creative period had passed. And it wasn't that he was never coming back. He just didn't want to come back before they'd accomplished as much as they could with this interesting system. And so, when we came here, he still wasn't here, so we stayed in his house for--I guess his wife was in Cambridge, too--and we stayed here at his house, and Gary came to the lab as well about that time. Jack Dunitz , who was a very well-known small-molecule crystallographer, worked in Zurich most of his life. He had gone back on the boat that I came across on, so I never saw him again until later. And he decided he would only stay for one year. He wasn't really interested in working on the things that Alex wanted to work on. Just about this time, Marianne Grunberg-Manago, who's worked at the NIH quite a bit, and Severo Ochoa, discovered the polynucleotide phosphorylase. This was an enzyme that made polymers, starting--it didn't start with ATP or anything like this. It started with ribonucleoside diphosphates. And it didn't have a template, but it would, if you gave it ATP, it would, ribo ATP, it would just make polyricinoleic acid. If you gave it UDP, it would just make poly U and poly C. It was difficult to get it to make poly G. So, Alex went--first I think he talked to Ochoa, and then Ochoa gave us some of the polymers. And I think one of the first things that we discovered was that, if you mix them together, you got a diffraction pattern that clearly resembled DNA, and so you could take poly U and poly A and mix them together and they would form a double helix. It may sound totally trivial now, but at that time there was a real question about this. There was a man Robert Warner, as I recall, in New York who had, looking at sedimentation coefficients, and said that this probably would happen.

Park: When your group was working on this topic, did you have in mind some kind of DNA-RNA interaction?

Davies: No. I think what we were thinking of at that time was that the structure of DNA was known and that there would be something perhaps equally interesting in RNA. Instead, what we really found, I think, was that you could get an enormous variety of base interactions. For instance, one of the things that we did, I think I mentioned before, with Watson and Crick was we determined the structure of poly A. So, anyway, there was Ochoa and Marianne Grunberg-Manago. It was Marianne who had worked at the NIH at one point, but I think this was prior to that. This was before. I think she went back to France and then she came back here to stay.

They had this polynucleotide phosphorylase, and Alex managed to get the polynucleotides from them, and then you could pull fibers. And the reason that we were collaborating with Watson and Crick was that Watson had pulled some fibers which gave an unusual diffraction pattern, one that you couldn't explain. This was for poly A. And eventually, we worked out what the structure was. And I think Frances Crick helped Alex, myself. And the adenines were arranged, were pairing together. It was two strands. The adenines were pairing together in a way that you would, had not been seen in the Watson and Crick structure and in a way that resembled the crystal structure of adenine hydrochloride, which had been determined and which I knew about as one of the very accurate structures that had been done in Cambridge by Bill Cochran and [unintelligible]. And so, on the one hand, you learned more about double-helix structures and that RNA could form a double-helix structure like DNA, but, also, we were learning about the possibilities of these structures combining with themselves, like poly A, where you had two strands, each with adenines on it, and it was very exciting, I must say. So then we discovered... Well, we discovered the triplex.

Park: Before the triplex, you found the double-stranded structure of...

Davies: Yes, right. And the triplex was--really, the clue for the triplex came from Gary Felsenfeld's very careful work on mixing curves, and he made these mixing curves where he measured the optical density and he varied the percent of U from zero to 100 and the percent of A from zero to 100 going in the opposite direction, and he was trying to get two perfectly straight lines which would show that the reaction was sort of reversible, and it's what he was expecting. Instead, he found that there was a bowing of the curve at the high U end. And one day, he realized that if you extrapolated, you would come down--and drew a straight line--you would come down and you'd meet the other straight line at 2:1. And so he asked me if I could build a structure of this, of the third strand, and of course I went and looked at the model we had in the next room. And, of course, we realized right away we could do this. And that was the triplex structure. But then Alex came and Alex was able to show that if you added magnesium--at least Alex and I together, I'm not sure--if you added magnesium, then instead of having a bowing, you got two straight lines that met at 2:1. And so the magnesium was stabilizing the triple helix. A triplex structure like that has a lot of negative charge, and it's filling in the broad group of the DNA.

What else did we discover at that point? There were other things. But those were the major things, I think.

Park: How was the idea of triplex received by scientists?

Davies: Well, people were impressed. It was exciting for us, but we couldn't find any real rationalization for it at that time. And we couldn't see any biological advantage or usage of this because it was just poly A and it was just poly U. Now, later, it was shown--I think this was done to some large extent by Mike Chamberlain--it was shown that you could take G on one strand and C on the other strand, and I think this was done with DNA and polymers. And if you charged the C, if you put a proton on the C, then you could get it to bind in the same way and you could form a triplex G-C structure where you had G's and then one C. What Watson and Crick did with one C around this side. And, of course, by that time, people were calling it the Hoogsteen structure. And basically what happened was that [Karst] Hoogsteen did the structure of two bases, the crystal structure. This is several years after we'd done this with the triplex. He did the structure of adenine with uracil or methyl adenine with methyl uracil, with a methyl where the sugar would be, and it formed this backside structure to the adenine with hydrogen bonding. And he wasn't aware of the fact that we had suggested this before, and so this became known as the Hoogsteen structure. And the C will form exactly the same arrangement as long as it has a positive charge on it. So the positive charge helped it to bind to the -oxygen and the nitrogen of the guanine. One of the reasons that Hoogsteen might not have been aware of this was that, when we published the paper of this structure, we published it in JACS and I think I mentioned this before, they wouldn't let us put in the picture of the structure.

Park: Yes.

Davies: They made us take it out because they said the paper is too long. It was unbelievable.

Park: Actually, it's a short paper.

Davies: Right, right. I think it was I never went back and published the structure that we cleaned up. So that was that. And we had a wonderful time. I mean, there were lots of new things to discover. So the time went quickly anyway. In about three years, Gary went to Pittsburgh as a professor there, and Alex Rich went to MIT. He tried to get me to go to MIT, too, but I decided to stay here. I liked it here.

Park: What aspects do you like most here?

Davies: Oh, I like the fact that we got...

Park: Did you miss the university?

Davies: Yeah, to some extent, but not all that much, because, you know, I was still working on my own. don't know really how American professors manage in the sciences, particularly in their younger days. I mean, they have to teach, they have graduate students, if they're lucky they have some postdocs, and they have to apply for money, they have to do all sorts of things that you don't have to do here. And even though I taught--I did teach in a graduate school; I still do, in fact--it wasn't mandatory and I didn't have to do it. And, I mean, it would have been nice to have had some graduate students later on, but at that time, it was just right for me, I must say. So we were over there in the Mental Health Institute, lots of really great people over there.

Park: What was your status as a postdoc?

Davies: I was a visiting scientist.

Park: Visiting scientist?

Davies: Right, right. And we didn't get paid very much. I think my starting salary was $7,500 a year. But it was enough to live on. And then Alex left and I decided not to go to MIT, to stay here, and then our lab went through a period, a mixed period. I worked on a number of different things. One of the things was the binding of dyes to DNA. There are these acridine dyes, like profilin and acridine orange, that bound to DNA, and we looked at diffraction patterns of these and tried to see what we could learn from those, and we learned quite a bit, actually, that the dyes were actually going, slipping in and inter-collating between the base pairs of the DNA. Then, at that time, in 1959, I went to Cambridge for six months, and that got me much more thinking about proteins. I worked... Did I talk about this last time?

Park: Yes.

Davies: Well, you know, the Cambridge lab was this was the Medical Research Council lab, and to learn more about it, Perutz has written a number of books. It was a little Nissen hut at that time just in the Cavendish Laboratory Square, in the inside, not terribly long, one story. On the right-hand side, there were the offices; on the left-hand side, there was a relatively small lab, and it had John Kendrew, Max Perutz, Frances Crick, Sydney Brenner. It had all sorts of people in it, and it was really fantastic. So, John Kendrew, who had an office as big as this little room, shared it with me. And I was going to go there to work on some myoglobin structure, but by the time I got there, they were way behind in their schedule, and so they were still working on the two-angstrom structure. And they had Rossmann, Strandberg, Dickerson. I'd been there for at least a year. I think Strandberg had been there for two years. And they were just reaching the stage where they were calculating the electron-density map. It was very exciting. It was two-angstrom resolution. And they'd just about finished collecting the x-ray data and measuring it. They had a team of young women who measured with densitometers the intensities on the films that Dickerson and Strandberg were taking.

Park: Densitometer?

Davies: Yes, a micro densitometer, so that it would scan along the row of spots in the film and record the intensities on a piece of paper, and they would measure these intensities with a ruler. They would have to index their reflections, HKL, and then they would write it down. And Kendrew used to check this, and it eventually all ended up on paper tape. And there's a picture. I've seen it on screen, but I'm not sure I've ever seen it published anywhere. There's a picture of Strandberg and Dickerson carrying a long pole over their shoulders, and hanging from the pole are thousands of paper-tape strips with the intensities on them. And the interesting thing is that they both wore jackets and they both wore ties, because that was the way things were done in those days. And Dickerson probably has that slide. I'd like to get a copy of that sometime. One night, Cambridge had this EDSAC 2 computer, and I think I mentioned before that Max... The MRC lab always had the very latest stuff, but they were very fortunate because there were only one or two electronic computers in the world, and one of them was at Cambridge, in the math lab. And so one night they got permission to use this, and they decided to calculate the electron-density map. And I remember it very well. I went along, although I hadn't really contributed very much up to that point. I went along, and various other people. David Phillips came down from London, and Vy Shaw [sp.]. She had been helping. They'd collected one of the data sets. And Dickerson and Strandberg were trying to get, make sure the program worked properly, and time went on and it got to be about one o' clock in the morning. And finally, they decided everything was okay and they calculated a section through the hemoglobin, and there was a big peak right in the middle, and that was the iron. And so everybody knew that it would be okay. And in the course of the next few days, they calculated all the sections, and then gradually--then the question was, what do we do with this? And Kendrew went out and he decided that he would build a large model using the model's five centimeters to the angstrom that Pauling had devised for the alpha helix.

Park: Yes, yes. I guess I have a picture. That paper.

Davies: Well, I can show you the picture of Kendrew himself. I've got a slide of Kendrew by himself. There's Kendrew and Perutz. And you can see... Strandberg and I went out and bought these plywood, big thick plywood sheets, and we bought a drill and we drilled holes, and then we stuck in these steel rods. And then we took these little clips--they were little erector-set clips--and we color-coded them according to electron density. And then, here's an alpha helix, for instance. You can see it running up here. And Kendrew started putting these into the model, and you could move them apart because each board was about this wide and about six feet or so long, and it occupied a lot of space. Let's see. It was about 30 angstroms in diameter, 30 plus, so, fortunately, it was a small protein. And so there was a 30 at five centimeters to the angstrom, so that's quite big. I mean, you can almost getting on for two meters by the time you go all the way around, and it took up a room.

Park: I am interested in, in what stage of your research do structural biologists construct the model. I mean, when Kendrew and Perutz construct this kind of model, did they construct those models in mind first and have a pretty good understanding of what's going on and then have a confidence, and then let's make a model to see each other's, or whether you are finding something while you're making models.

Davies: Well, I'll give you... I mean, I wasn't involved in that early work, but I'll give you the best answer I can. Perutz wrote a book called *I Should Have Made You Angry Sooner*. Have you read that? He sent me a copy and so I've got it. Read it sometime. And I've already read bits of it, but I've heard him talk about the... It's on the talk that he gave at my 70th birthday thing. Perutz talks about this. So Pauling proposed the alpha helix in 1951. In 1950, Bragg, Kendrew, and Perutz had proposed a helical structure for peptides, polypeptides, which was very close to the alpha helix, made the alpha helix type of hydrogen bond. I mean, it's what you would call topologically practically identical, except that it had a fourfold screw axis. It was an exact fourfold whereas the Pauling structure ended up as 3.6 residues per turn. This had four residues that covered one turn. And he also, they also bent the peptide bond. And I remember Kendrew telling me once that this was--they had gone to ask a very distinguished Cambridge theoretician whether they should keep it planar or not, and he says, "Oh no." But Pauling knew from his results and from his calculations that this would have to be, the peptide bond would have to be planar. So it was an additional touch that he put into the alpha helix. Without that, he couldn't have gotten the right structure. So they had had a structure which was similar to the alpha helix in many ways but wasn't the alpha helix, and everybody accepted this. And they were so annoyed that... And at the same time--again, I refer you to the Perutz lecture--they had been calculating, Perutz had been calculating electron-density maps or what they called Patterson functions. It's the function that convolutes the electron density with itself. And he showed fairly strong evidence that there were broad structures. And I think I mentioned, I think it was 1951, we went to Cambridge to this meeting with David Sayre and various other people from the Oxford lab, and at this meeting Perutz presented this structure for hemoglobin in which all of the helices were sort of parallel. And then that's where Crick got up and said that this was impossible because it didn't give the right Patterson function. And we'd never heard of Crick before, but he certainly made a big impression because he was much older than the rest of us students. He was Perutz's student. And he had been through the war. He had been taking a Ph.D. for several years before the war, and so he'd been through World War II and he was very sophisticated by our standards. And so, helices were all around. I mean, people were thinking in terms of these things.

Park: In the air.

Davies: Right, in the air, exactly. But I guess the next thing that happened was that Kendrew and some early collaborators determined the structure of myoglobin at six-angstrom resolution. It was either five or six. And they could see rods going in various directions, not all parallel to each other. And they assumed that these were alpha helices. And Perutz was able to show, in 1951, I think, or '52, he was able to show that the alpha helix would give you a reflection at 1.5 angstroms if you tipped the fibers. And this reflection was there. There was a region of high density in that region for proteins like hemoglobin and myoglobin. Now, we'd have to check the exact references to these, but that's my recollection. And that's why Bragg said, you know, and he did it because he was so annoyed at himself for having not predicted the alpha helix, and that's where the line, "I should have made you angry sooner," is what Bragg told him when he described how he had shown that there was pretty strong evidence that the alpha helix would exist in hemoglobin and in myoglobin. So--but no models were built at this point, I mean, apart from the simple models of the alpha helix. And then, when Kendrew got this map and started building this thing, it turned out that, I mean, he was just following the electron density. He knew what the sequence of the protein was, so he knew which amino-acid side chains to look for. And you could pick on, say, a tryptophan or something like this, which would be a big planar side chain, and you say, "Okay, this must be, this could be"--I don't know how many tryptophan's there are in my building, but say there are two--"this could be one of two possibilities." And then he'd look at the next amino acids, and from there he'd be able to tell where he was in the sequence. I'm not sure that that's exactly how he did it. He may have gone straight, built all the alpha helices first, and then looked to see how things were. When I was there, we did one thing before the model building. Dickerson, I think, had gone back to the States, and Strandberg was on vacation in Sweden, and John Kendrew and I decided to look at one of these rods. We took a cylindrical section through the rod and, fortunately, we picked one of the right ones. And so what we did was we--there were all these planes of density, so we took ellipsoids because everything was going through obliquely, and we calculated, we put each of these ellipses down on top of the density for that plane, and we contoured. We got contours for them. And then we looked, then we unfolded the whole thing in the end, we contoured everything in, and there was an alpha helix, and it was one of the alpha helices that we published in that paper. So that showed for the first time that you could actually see in the electron-density map an alpha helix. So that was a big thing. And Frances Crick rushed in, and he had a theory of how proteins folded, and from the C terminus, as I recall, and it was very exciting. But then, afterwards, to finish the whole thing off, Kendrew had to build this huge model of, what is it, about 160 or so amino acids of the heme group. So nothing was done from--it was totally different from working with nucleic acids. The nucleic acids, you got a primitive diffraction pattern from which you really couldn't tell a great deal. You could tell roughly what the helical dimensions were, and you assumed it was a helix that was giving rise to this. That's true for collagen and for polyproline and for DNA and for the alpha helix, but in this case, you had to have the electron density. And what you did was you just traced the chain to follow the electron density, so if red was the high color code for the high density, Kendrew just followed the red clips on these rods and traced around as best he could--helped by the fact that we had looked previously at this rod and shown that it was really an alpha helix. See, once you did that with the thing that we did together, you knew which was the N terminus and which was the C terminus, but you didn't know before. See, when you just had the six-angstrom map, you didn't know which was the N and which was the C. You also knew that you had drawn it up with the right hand. Do you understand?

Park: No.

Davies: It gets complicated.

Park: Electron maps.

Davies: Right, right. That's the same thing.

Park: Yes, same thing.

Davies: And there should be a model. This was the original one. This was the six angstrom. They thought the heme group was here. It was actually oriented differently from this, but it was in this position. And these they interpreted as being alpha helices. And here it is. So, this is the helix, and you can see that you fit this with a helix just beautifully. Okay. Well, we did it and I knew a lot about helices by that time. So, not only did it have the alpha helix radius--we calculated the slender cone section alpha helix--we also did it at the beta structure. I mean, I'm sorry, not alpha helix, alpha carbon atom. We also did it at the position of the beta carbon atom, and that way we were able to see whether the amino acids that we were looking at were L or D, and they turned out to be L, but it could have been D, and the actual structure could have been the mirror image of this. So it was quite exciting to do that. And I came back here and continued for a while to work on oligonucleotides and polynucleotides. Let me go a little bit further. So, I started to work on proteins.

Park: Right.

Davies: Yeah, probably in 1960 or so. And the protein that I chose at that time was a form of gamma-chymotrypsin. It's called gamma-chymotrypsin and I chose it because it gave beautiful crystals, you could buy the protein by the pound, and it really did crystallize very easily. I also looked at lysine, which is also a protease, but a somewhat different one, and I had beautiful crystals from that. And Sid Bernhardt, who was the head of my section at that time--he'd taken over from Alex Rich--he dissuaded me. He said that when he ran this through a column, it was all broken up. It was auto-digested. But I should have stuck to it. I should have gone with the lysine because it turned out that the MRC lab had a project on chymotrypsin. It was a different crystal form. It was called alpha-chymotrypsin. And with David Blow, and who was here quite recently, actually, and they had an infrastructure, I mean, there was no way you could compete with those guys. They were really very well set up. And, of course, they came out to the structure long before we did, but I was getting interested in proteins. Then we moved. The NIH was, you know, it was a very friendly place, very collegial. I mean, you met lots of people. I wasn't that much of a party person, but you really met a lot of people.

Park: How did you interact with other biochemists here?

Davies: Well, I knew relatively little of biochemistry at that time because I was still suffering from my physics background. It took a while. And so, I used to travel in a carpool--I think I told you this--with Gordy Tompkins, Dyda and Cunliffe. We all lived in the same part of Kensington. We used to drive in in a carpool. And so I got to know those three very well. And Gordy especially was fantastic, and he and Hans Stetten decided to set up the Laboratory of Molecular Biology, and Gordy was talking about this, and he was going to bring Gary Felsenfeld back from Pittsburgh. He wondered if Gary would be interested in joining the group. And he invited me and he invited Harvey Itano, who I think was in the Heart Institute. Harvey was the person who had shown, along with John Singer, that sickle cell hemoglobin was different from normal hemoglobin, and he invited Bruce Ames . Bruce Ames is very well known now. He's at Berkeley. And he was doing work on the histidine enzymes of the histidine operand to see whether carcinogens were also mutagens. That was his hypothesis. And so, who else? We've got Bruce, Gary, myself, Gordon, Harvey Itano. I think that was it. They were the five people who were going to be the section chiefs. And we tried to get Marshall Nirenberg to come over as well, he had just discovered--this was in 1961-62--he had just discovered the code, and he was such a hot commodity. We didn't have the space to set him up, and he decided to go into the Heart Institute, because he had been in Gordy Tompkins's lab when he discovered the code, and a really fantastic breakthrough. And you've no idea how it changed people's thinking, you know. Overnight, people went from thinking, "Well, I'll work on this protein and...."

Park: People's thinking here at the NIH? Or all over the country?

Davies: All over the world. And, you know, "I'll work on this protein and I'll look to see what mutations occur in it, and I'll do the amino acid sequence, and then gradually I'll look at the nucleic acid and gradually I'll learn something about the code." And all of a sudden, out came the code, from Ochoa's work and partly, but mostly from Nirenberg. There was a lot of support for Marshall at that time. People really banded together to make polynucleotides for him and discuss his results. It was very exciting.

Park: The support, you mean not administratively but intellectually among the scientists.

Davies: Among the scientists, and not just intellectually, but in terms of giving him materials.

Park: I see. The Laboratory of Molecular Biology was composed of five section chiefs coming from...

Davies: That's all I remember now.

Park: I think that's right. I have documents about that. So you, from Mental Institute.

Davies: From Mental Health, right.

Park: Yeah, Mental Health.

Davies: Harvey from Heart, and Bruce and Gordy from the Arthritis and Metabolic Diseases.

Park: Right. So, from that case, it seems to me that there was no real institutional barrier between the institutions at NIH, among the scientists. I mean, they--if you're interested in, for example, molecular biology or protein, then scientists interact across the institutions. Is that true?

Davies: Yes. It wasn't that we interacted all that much. It's just that we knew each other well, we'd go to parties together, and we enjoyed each other's company, and we respected each other as scientists. I think it was that more than anything else. So, the day that we moved, Marie Lipsett called me up. Now, Lipsett is a well-known name around here because of Mort Lipsett. This was Mort's wife. And she worked with Hepple. I mean, there was a lot of infrastructure here in terms of what was going on, and Hepple --you've probably heard of Hepple. Right?

Park: Yes.

Davies: Yeah. He worked on polynucleotides, and I'm not sure what all the people in his group did with polynucleotides, but there were a lot of things going on, and Maxine Singer was one of the people in his lab, and so was Marie. And we had talked a lot about polynucleotide structures. And so, the day that we moved--we were moving to Building 2 to start this new lab--she called me up and she said, "David," she said, "I've got something that you'll really be interested in." I said, "Marie, for God's sake, we're moving. All the x-ray equipment has to be moved and everything." And she says, "Oh. Well, I thought you'd be interested. I've got some poly G." Well, as I mentioned before, we'd never been able to get poly G before, and it's one of the mysteries. And so I dropped everything, went into the cold room, pulled some fibers and left them there, and then went on with my moving, took an hour or so off. And then about a month later, she called me and she says, "What did you ever do with that poly G I gave you?" So I told her that I'd forgotten all about them. They were still in the cold room. And she said, "Oh. Well, don't bother." She said, "That wasn't poly G after all, it was GMP." Well, you know, I was so excited by this, I ran all the way over and found the fibers, and it turned out that you could take just GMP and it would form a helical structure and you could pull fibers from it, looked just like DNA, and you had to cool it down a little bit. But if you cooled it down, you could pull fibers from it, and the fiber diffraction pattern indicated fairly clearly to someone like myself that the structure had to be a tetraplex structure, and that's the structure that people have since seen for telomeres, where you have the rich, G-rich regions forming these things. But we had no idea at the time that it would have any biological relevance, except that just GMP, it doesn't matter which isomer you take, you just have to lower the pH to about 6, keep it at a reasonably low temperature, and it will form a viscous solution just 10 milligrams per mil, and if you warm it up, it behaves like an ordinary monomer again. But it is a monomer. It's not forming a covalent linkage. It's just that the G's are stacking on top of each other. So that was one thing. And I did that, actually, with Marty Gellert as well, who was in my section at the time.

Park: How was the section composed of? You as section chief. And did you have postdoc fellows or other staff members?

Davies: I was the section chief, and Marty Gellert had a room in my lab, and we collaborated on various things. We had previously written what I think is still a very nice paper on the orientation of DNA in phage heads, bacteriophage. And Marty, of course, has done extremely well since then. I mean, he's downstairs. He's very distinguished and continues to do wonderful work on antibody-gene recombination. And so we did that. It led--one thing led to another. We did the structure of poly G. We showed that poly I, which was a structure that Alex Rich had proposed, which was three-stranded and couldn't possibly be three-stranded because G can't be three-stranded, and I gave the same diffraction pattern as G, and that was really the last thing I think I did on nucleic acid. So we went on to the mid-'60s or so. And at the same time, I was beginning to develop this program on protein structure, which was a totally new thing for me.

Park: Before going to the 1960s and your protein work, I want to ask you about the reputation of NIH in the 1950s. And this is the book written by Horace Judson. Have you read this?

Davies: A long time ago, a very long time ago.

Park: And it has a lot of information about the lives of molecular biologists of the time, and it has a description of Marshall Nirenberg at the NIH, and let me read a little thing about the description of NIH at the time. "Marshall was not on the grapevines. It wouldn't have been his personal inclination to talk about anyway. He's not that way, not since single-cell. There was no reason why anybody should have known about Marshall. He was one of these young, new NIH crew. At the time, NIH didn't have the reputation as a scientific institution it has now. The impression people had was that it must be just another government one-shot sort of thing." So Marshall was very much not part of all that, and he did not come out of the phage group. And he talked about Marshall's kind of science.

Davies: The phage group fairly dominated a lot of early molecular biology, people like this.

Park: I was wondering, this kind of impression about NIH at the time as experimental.

Davies: Well, no. It was a very small place until we built the Clinical Center, and they built the Clinical Center--well, I think the first people moved in probably in '53 or '54, and so it was just establishing itself. And there were lots of very good young people around, and many of them came here because of the draft. They wanted to satisfy their draft obligations at the same time without going into the Army.

Park: Alex Rich was one of them?

Davies: Alex was an M.D. He would undoubtedly--he was in the Public Health Service, so almost certainly for the same reason. I mean, everybody who came here did that, all the M.D.'s for sure. I mean, over the next few years, when we went through the, into the Nixon period and then we had--it was the doctors' draft, and we got many of the best M.D.s in the country coming here. I mean, if you were really bright, it was terrible to have to think of going into the Army when you could be here and doing research. Paul Sigler worked with me when we moved over to Building 2 . Paul came just before we moved. Do you know Paul Sigler? Have you heard of him? He's a professor at Yale, doing fantastically well. He's one of the best, most productive crystallographers in the world at the moment. And he's big, with a loud voice, and he interviewed me, or I interviewed him--I'm not sure which it was--when we were over there in Building 10, and he wanted to work with me on protein crystal structure and so on. He wanted to work on structure. He was very much interested in chemistry. And although he had an M.D. degree, and he had not only got his degree but he'd gone through his internship and his residency at Columbia, so he was full of stories about medical life and patients and things, and he talked for about an hour. And after the end of the hour, I said, "Well, you know, Paul, if you come work with me, you'll probably never see another patient in your life." But he didn't care. He was determined to go into this structural stuff. So he came and worked with me. And first of all, he worked on a nucleic acid experiment and the reaction between a double-stranded polynucleotide and a single-stranded polynucleotide and how they would exchange strands. And then the other thing he worked on was, he started work on the structure of gamma-chymotrypsin with us. And then he went to Cambridge and worked for David Blow, where he took a degree, took a Ph.D. in crystallography. So he was one of the first people I had as a postdoc. And I hired several other people, I hired a technician; Braxton and gradually, people came to the lab and we made do with them. Charles Coulter came. And then gradually there was beginning to be turnover, and one of the nice things about the NIH was that somewhere fairly early on, they developed a system of fellowships so that people who came here... Up to that time, anyone who came here went into the civil service, and after one year in the civil service, they had tenure, see. I mean, you can imagine what would have happened to this place if you hadn't abandoned that system and developed the system of fellows, where people did not have a permanent job, I mean, unless they were very special.

Park: To satisfy the military obligation and then get tenure?

Davies: They didn't have tenure. No. There was no guarantee of tenure at all. I mean, most people, it was assumed. They were, they're called staff fellowships. For the M.D.s, they were called clinical associates or research associates. And they were, I think, two- or three-year appointments. They could be extended, but it wasn't intended to extend them by very much. And that's what saved the NIH, and that's why it's still a great institution. And if they hadn't had something like that, if everybody who'd come and worked here had had tenure, we would have been dead by now. We'd be locked in concrete.

Park: So, for example, to get post-doctoral fellows, did you advertise the announcement or did you try to get people from universities?

Davies: Well, nowadays we do that. Certainly, by the middle '60s, I was doing that. Yes. Initially, a lot of it was accidental, like Paula showing up. I went out to look for a technician and acquired her. Cathy Skinner worked with me. I don't even remember how I encountered Cathy. She was a mineralogist. I mean, see, there weren't any people around who knew protein crystallography. I mean, that's what you have to realize. And there was nobody. And so you tried to interest people who had worked on small molecules. Eventually, I did hire Gerson Cohen and Enid Silverton. They both came about the same time, in 1965 or '66. But they were small-molecule crystallographers, and they gradually got interested in proteins.There were relatively few people who went through Cambridge and worked with Kendrew or Perutz, and that's where the real training was at that point. And relatively few of these, I mean, none of them would be looking for a second postdoc. I mean, they'd be looking for professorships because they had such unique knowledge. Brian Matthews came to work with me. Now, he had been in Cambridge and he'd worked with Paul Sigler and Blow on the alpha chymotrypsin structure. He came here just after that, probably about 1968 or so but Brian was recommended by Paul Sigler who had known him in Cambridge, and he was an Australian who had gone to work with, also worked on small molecules, and he knew of the early work that I had done because they had--when he was a graduate student, we had worked on the same structure, and so he was aware of my work. Well, within a few weeks of his being here, he got job offers. I mean, people were beginning to realize that this field of protein structure determination was a hot field, and they all wanted to get people with experience in it. And they offered him a job at Duke, I remember, and Brian decided to stay for a while, and then Oregon, which had been trying to recruit me, and I decided to stay at NIH, they offered Brian a job, and so he went. He's been there ever since. He's done very, very well.

Park: How many times did you get an offer from the university during your tenure?

Davies: Oh, many times.

Park: Many times.

Davies: Yes.

Park: Have you ever seriously considered moving to academia?

Davies: Well, the closest I ever came was moving to Oregon. But, no, I don't think I ever seriously considered it otherwise. It's hard, you know, to pick up everything and move, and all my friends are here. I'm going to have to go down the hall for a second. I'll be back in just a second.

Park: All right. It's about the Laboratory of Molecular Biology in 1961.

Davies: I think it was '61. I'm not sure exactly when we moved into Building 2. I think it was '61, yes.

Park: And this is a memo by James Shannon approving the creation of that laboratory, and I was lucky to find this document. And here you see that the expiration. I think it resonates with your comment that the protein chemistry was becoming a hot field, and it seems that, at the administration level, that importance has been recognized.

Davies: I would say yes. That's very perceptive, more or less, and it's absolutely true. The molecular understanding of things was beginning, just beginning to take over, and to make it felt, not take over, just beginning. And it was clear, you know, up to that point, a lot of people here worked on enzymes, but they were mainly interested in kinetics and stuff like that, what the enzyme did and what the kinetics or the reactions were. And there were a lot of very good people, I mean, who discovered interesting enzyme systems and did great things with them. Arthur Kornberg was here at one point.

But this new field, molecular biology, as we then called it, was a totally new approach to these things, I mean, thinking of things in molecular terms always, even though you might still be doing many of the same old experiments. But if you could get a structure for an enzyme, then you could begin. You would learn so much more about the mechanism of action.

Park: Right.

Davies: So it really was. Yeah, I would agree with that. I think that's quite perceptive to say that.

Park: And you mentioned, there were sections.

Davies: That was Gordy's.

Park: Right. Chemical genetics.

Davies: That was Bruce Ames. No, no, no, this was Bruce Ames, chemical genetics. That must have been Harvey Itano.

Park: Right.

Davies: This was Gary and this was me.

Park: And how did these sections cooperate or exchange information? Did you meet regularly?

Davies: Yes, we did.

Park: Could you describe the kind of daily life?

Davies: Okay. Well, we had, once... The building was small. You know, we occupied two and a half floors in the building, second floor, third floor, part of the attic, and the x-ray equipment was up in the attic. It was almost the only stuff up in the attic. So you would bump into people all the time, and it was much smaller than this building. This building is big and it's got a long corridor.

Park: Their building is Building 2?

Davies: Yes. And you don't see so many people out in the corridor as you did in the other place. So we'd always be meeting and chatting and talking. But, in addition, we had a journal club.

Park: When did it start? Right at the beginning of the Laboratory of Molecular Biology?

Davies: Yes, right from the start. And I think it was based on a journal club that they had over in the Hepple lab, which was originally started by Arthur Kornburg, I was told. And years after Kornburg had left, when people would--they used to have a journal club every lunchtime; somebody would have to present a structure, and people complained that it was too much and they wanted to cut it back. And the response was always, "Well, Arthur wouldn't like that." It shows how strong his--if you ever meet this guy, he's fantastic, and he's got such a strong personality.

Park: I see.

Davies: Arthur wouldn't approve, years after he'd gone. And so, we had a journal club. I think we met--I don't remember. You'd have to ask Gary this, or Marty. I think we met twice a week, and then at least once a week. Once a month, but maybe even once a week, we would share seminars and people would report on what work they were doing and various other things. We would have guest speakers and all that kind of thing.

Park: This is in addition to the section meeting?

Davies: There were no section meetings. At least I didn't have any because my group was so small and I talked to them all. And we used to have lunch. For a while, we had lunches together up in the attic of Building 2--a lot of us, not all of us. But eventually that broke down. The lab got bigger. We were sharing the lab with Chemical Physics, and Chemical Physics in those days was still a spectroscopic lab. And there was this guy Bracket there. I told you that story, didn't I?

Park: No, no, you didn't.

Davies: Well, there was Brackett there, and I was astonished to discover that this was the Brackett whose series in the hydrogen spectrum I' d learned about when I was a physics undergraduate, and I couldn't believe that he was still alive. It turned out that he'd done this work when he was a graduate student, and then he came to the NIH and he worked here for many years. And he worked, I think, more on biological spectroscopy, and the physicists thought that he had died. And so when they went around the moon and saw the other side of the moon, they started naming craters after various famous scientists, and they named one after Brackett, thinking he was dead. And there he was. There's a picture of him downstairs--you should see that--pointing to his crater on the other side of the moon.

Park: Interesting.

Davies: So, I mean, there was a man called--oh, what the hell was his name? I talked about this in that talk I gave, which you have a recording of.

Park: Yes, I have the transcript.

Davies: What was his name? I'm blocking on it. Ralph Wyckoff.

Park: Wyckoff, yes.

Davies: And he was a crystallographer who worked in Building 2. I never had much contact with him. He was really more interested in developing what eventually the crystallographers took over as something they called structure reports. But he had his own crystals, compendium of crystal structures, and I think they were in loose-leaf folders, and they contained all the structure information about small molecules up to that point. And he was also doing electron microscopy, and he was quite distinguished, I think. He--I don't even know what he did altogether, but he was for a time, when he left here, he became the science attaché in London, for the embassy, and then eventually he went to Arizona, and I think he was there for a long time. So there was someone there who had been here for some time who did structure, but it wasn't structural biology. And like Bracket, Billy is the person to talk to about Brackett. But I couldn't believe that this was the same guy.

Park: Did you have some interactions with the chemical physicists?

Davies: Not immediately. I knew Elliot Charney very well. He was down in that lab, and he was a wonderful, very nice person. And eventually, I'm not sure when, Billy came to work with him, and Billy used to come up and talk to me a lot in those early days. See, it was hard for him, Bill, to adjust, you know, he'd been in an academic. He was an M.D. and a Ph.D. and he'd been in Penn all his life, all his academic life, although he did go to Cambridge once and he'd also been to Berlin for a year. But it was hard for him to adjust to the atmosphere here, which was more just working and no students to speak of and that sort of thing. He felt sort of out of it.

Park: The life of research.

Davies: The life was just research, and it's not that Bill didn't like that, but I think he missed the academic environment. And I think he particularly missed Penn, which he liked very much. But he's done a fantastic job there.

Park: At one point you mentioned that you had kind of a tea meeting with the people in the laboratory to get together and discuss and...

Davies: My memory is going.

Park: It was a part of the journal club or you had center things.

Davies: That was in this building, Building 5. We had tea for a long time. Twice a week, we would meet for tea down on the second floor, and Chemical Physics and Molecular Biology would meet.

Park: When was that? What year?

Davies: Oh, from the time we moved in--it fizzled out about a year ago. People just lost interest because, you know, there were regulars like myself and Gary Felsenfeld, a lot of Gary's people because their labs were right across the hall from the tea room. And a number of people like Marius [G. Marius Clore] and Angelo would come down, Bill Eaton would come from the lab down below. But then Bill backed out of it, and gradually we just let it die and we stopped doing that. The thing is, if I may say so, that when we moved into Building 2, everybody knew and understood what everybody else was doing. Now, maybe we were more mentally agile at that time, but the field was also much smaller. There wasn't so much to know and there wasn't the degree of specialization that you have now. It's enormously complicated now.

Park: In Building 2, there was the Laboratory of Molecular Biology.

Davies: Yes. I don't know whether they were called Chemical Physics. They might have been, although I think that might be a new name.

Park: That's interesting. And as the field grows and also the NIH grows, it's kind of difficult to manage everybody's progress in research.

Davies: Oh, you can't keep up with it. You can't. There's no way you can keep up with it. It's become so much more specialized. I mean, look at the structures. We just had our review.

Park: How long do you think that that kind of close communication lasted, continued?

Davies: Well, it lasted for quite a few years.

Park: In the 1960s?

Davies: Of course, I'll tell you one thing. Gordy Tompkins and I used to talk in the carpool all the time about research, and Peter Cunliffe who was one of the other people in the group, in the carpool, once said, "Well, you and Gordy were talking to each other all the time, and neither of you understood what the other one was saying," which was not true at the beginning. It may have become more true later on, but it certainly wasn't true then.

Park: When was the critical time?

Davies: In the early years. Oh, it's hard to say, it's hard to say. You know, as we all got somewhat larger groups to work with and we were in competition with groups all over the world, I mean, when we worked on the polynucleotides, I mean, we had the field to ourselves. It's hard to believe, very hard to believe. It's totally different from now. If you have an interesting topic now, you know that somewhere in some lab, somebody else is doing the same thing.

Park: But at the time...

Davies: At that time, that wasn't true. You knew what everybody was working on.

Park: Right.

Davies: It was--we were lucky to be in that period. We were very fortunate.

Park: And do you, did you feel that kind of the beginning of the so-called golden years at NIH is the period between 1955 to 1967, when the NIH project took off and James Shannon kind of protected the basic science and basic scientists? It was often described as the golden years. And when you came here and started working here, did you feel a great momentum or a great change going on here?

Davies: No, no, because we were in the Mental Health Institute. We had a small lab there. Across the hall from us was Roscoe Brady. Do you know him? He's in the Mental Health Institute still. Neurology, maybe he's in neurology. And they couldn't understand him because he was working on fats. But he became very distinguished and very well-known from all that. He's a member of the National Academy. He's a wonderful guy. But we just had this small lab, and it didn't change from the time that we moved in there till the time that we left eventually. We had this wonderful director, Seymour Kety. He's a very important early figure in NIH, I think. And he left us alone, we worked on whatever we liked. And I well remember that he was replaced, he went off to Harvard, I think, eventually, and Bob Livingston came and was the director. And I think I told you that Bob Livingston one day comes into the office and says, "Alex, come and have lunch with me, and, David, you'd better come along as well." So we get down there and he says to Alex, "Now, Alex, tell me, how does your work relate to mental health?" And Alex managed to get out of it, but I didn't really relate. He was pure basic research. And Livingston didn't try to do anything about it, but the mere fact that he asked that question was a little disturbing. And I think one of the things that really attracted me to this place was that there was no attempt to coerce anyone into working in any particular area, but the scientists decided themselves what they wanted to work on and what was interesting. So, in that sense, I mean, that could have been the beginning of the golden years because I'm sure if you back far enough before that, a lot of the direction was to clinical problems or medical problems of various sorts.

Park: Yeah. James Shannon's memo shows that.

Davies: That's a good memo.

Park: Right. Well, I think that we can stop here for today.